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(54) Title of the invention:

Local Anesthetic Composition

(57) Abstract

Objective:

To offer a local anesthetic composition that is both fast-acting and persistent.

Constitution:

A local anesthetic composition that uniformly and stably contains local basic anesthetic and hydrochloride thereof, formed by mixing local basic anesthetic dissolved or dispersed in an oil or fat or lipophilic base that is miscible therewith, and hydrochloride of the local basic anesthetic that has been dissolved or dispersed in solvent.

Effect

The composition of the present invention exhibits rapid and persistent local anesthetic action, and is stable, allowing its use as a topical agent for locally reducing pain and itching at the surfaces of skin injuries, such as cuts, scrapes, scratches, acne, impetigo and facial carbuncles, at skin and connective tissue sites such as hemorrhoids, heat rash, sores, rashes, hives, insect bites, athletes foot and ringworm, and at sites of tooth pain.

2. **Claims**

Claim 1. A local anesthetic composition that uniformly and stably contains local basic anesthetic and hydrochloride thereof, formed by mixing local basic anesthetic dissolved or dispersed in an oil or fat, or lipophilic base that is miscible therewith, and hydrochloride of the local basic anesthetic that has been dissolved or dispersed in solvent.

Claim 2. The local anesthetic composition according to Claim 1, wherein the blending ratios of local basic anesthetic and local basic anesthetic hydrochloride and the coefficient ratios determined by dividing the amounts thereof by the maximum allowable amount for the site of treatment are 7:3 to 2:3, and the sum of the coefficients is 0.5 or greater.

Claim 3. The local anesthetic composition according to Claim 1, wherein the local basic anesthetic is lidocaine, dibucaine, procaine, tetracaine, mepivacaine, chloroprocaine, bupivacaine, proparacaine, phenacaine, cocaine, oxybuprocaine, propitocaine, ethyl aminobenzoate, orthocaine or oxethazain.

Claim 4. The local anesthetic composition according to Claim 1, wherein the hydrochloride of the local basic anesthetic is lidocaine hydrochloride, dibucaine hydrochloride, procaine hydrochloride, tetracaine hydrochloride, mepivacaine hydrochloride, chloroprocaine hydrochloride, bupivacaine hydrochloride, proparacaine hydrochloride, phenacaine hydrochloride, cocaine hydrochloride, oxybuprocaine hydrochloride, propitocaine hydrochloride or diethylaminoethyl parabutylaminobenzoate hydrochloride.

Claim 5. The local anesthetic composition according to Claim 1, wherein the oil or fat, or lipophilic base that is miscible therewith, is coconut oil, palm kernel oil, camellia oil, olive oil, soy bean oil, sesame oil, corn oil, medium chain fatty acid triglycerides, cacao butter, laurin oil, tallow, hard fat, lanolin, beeswax, petroleum jelly, liquid paraffin, squalane, squalene, myristic acid, stearic acid, palmitic acid, cetanol, stearyl alcohol, 2-octyldodecanol, isopropyl myristate and octyldodecyl myristate, which can be used individually or in combinations of 2 or more types.

Claim 6. The local anesthetic composition according to Claim 1, wherein the solvent is crotamiton, water, propylene glycol, 1,3-butylene glycol, 3-methyl-1,3-butanediol, polyethylene glycol, glycerin fatty acid ester, sorbitan fatty acid ester, polyoxyethylene hardened castor oil, polyoxyethylene glycol fatty acid ester, polyoxyethylene sorbitan fatty acid ester or polyoxyethylene alkyl ether, which may be used individually or in combinations of two or more types.

3. **Detailed Description of the Invention**

[0001]

[Field of industrial utilization]

The present invention relates to a local anesthetic composition that has rapid and persistent action with respect to localized areas of the membranes and skin. In additional detail, the present invention concerns a composition that contains both local basic anesthetic and hydrochloride thereof.

[0002]

[Prior art and problems to be solved by the invention]

Local anesthetic is used in order to treat local itching and pain of the membranes and skin.

[0003]

For example, hemorrhoids, a localized affliction of the rectum that includes hemorrhoid sites and anal fissures, is accompanied by pain, itching, swelling, and bleeding of the affected area. Among these symptoms, pain at the affected area is the most agonizing to the patient. Thus, conventional hemorrhoid products have employed local anesthetic alone in a suppository or ointment, but their effects are generally inadequate because they are lost in a relatively short period of time. In addition, the remission of pain and itching at the surfaces of skin injuries such as cuts, scrapes, scratches, acne, impetigo and facial carbuncles, at skin and connective tissue sites such as hemorrhoids, heat rash, sores, rashes, hives, insect bites, athletes foot and ringworm, and at sites of tooth pain, is important not only from the standpoint of reducing the suffering of the patient, but also in regard to eliminating pain and itching in order to control behavior that will cause damage to the affected area via fingernails or external factors. Preparations in which local anesthetics are blended are used with these objectives, but the results have been inadequate because their effects are often lost in a short period of time.

[0004]

In in-patient prescriptions, two types of restricted local basic anesthetics are blended to produce eutectic mixtures, and although there are reports that physical irritation accompanying artery cannulas and injections is mitigated by ointments prepared using such mixtures, there are problems with the persistence and stability of the drugs.

[0005]

[Means for solving the problems]

The inventors of the present invention, as a result of painstaking investigations towards a solution to the above problems, perfected the present invention regarding a local anesthetic composition having rapid action and good persistence in order to reduce pain and itching at the surfaces of skin injuries, such as cuts, scrapes, scratches, acne,

impetigo and facial carbuncles, at skin and connective tissue sites such as hemorrhoids, heat rash, sores, rashes, hives, insect bites, athletes foot and ringworm, and at sites of tooth pain.

[0006]

The present invention concerns a local anesthetic composition produced by mixing a local basic anesthetic dissolved or dispersed in oil and fat, or lipophilic base that is miscible therewith, with hydrochloride of the local basic anesthetic dissolved or dispersed in solvent, where these drugs are contained uniformly and stably.

[0007]

Examples of local basic anesthetics include lidocaine, dibucaine, procaine, tetracaine, mepivacaine, chloroprocaine, bupivacaine, proparacaine, phenacaine, cocaine, oxybuprocaine, propitocaine, ethyl aminobenzoate, orthocaine and oxethazain, and examples of local basic anesthetic hydrochlorides include lidocaine hydrochloride, dibucaine hydrochloride, procaine hydrochloride, tetracaine hydrochloride, mepivacaine hydrochloride, chloroprocaine hydrochloride, bupivacaine hydrochloride, proparacaine hydrochloride, phenacaine hydrochloride, cocaine hydrochloride, oxybuprocaine hydrochloride, propitocaine hydrochloride and diethylaminoethyl parabutylaminobenzoate hydrochloride.

[0008]

With regard to the blending ratio of local basic anesthetic and local basic anesthetic hydrochloride, the coefficient ratio determined by dividing the amounts thereof by the maximum allowable amount for the site of treatment are 7:3 to 2:3, and the sum of the coefficients is 0.5 or greater.

[0009]

The maximum allowable amount for the site of treatment is based on regulatory standards. For example, Table 1 shows maximum concentrations of local anesthetics according to Manufacture (Importation) Permission Standards when the anesthetic is to be used, for example, as a topical hemorrhoid drug.

[0010]

Table 1

Maximum allowable blend amounts of local anesthetics.

Local anesthetic	Maximum concentration (%)
Ethyl aminobenzoate	10%
Lidocaine	3%
Mepivacaine	0.75%
Dibucaine hydrochloride	0.5%
Procaine hydrochloride	2%
Lidocaine hydrochloride	3%

[0011]

Thus, when 0.2 g of lidocaine hydrochloride and 1 g of lidocaine are to be blended in 100 g of preparation, the lidocaine coefficient is 1.0/3 = 0.33, and the dibucaine hydrochloride coefficient is 0.2/0.5 = 0.4. The coefficient ratio is thus 0.33:0.4 = 2.48:3, and the sum of the coefficients is 0.73.

[0012]

The oil or fat that dissolves or disperses the local basic anesthetic in the present invention, or lipophilic base that is miscible therewith, can be any substance that is used in the manufacture of common ointments or suppositories. Examples include coconut oil, palm kernel oil, camellia oil, olive oil, soy bean oil, sesame oil, corn oil, medium chain fatty acid triglycerides, cacao butter, laurin oil, tallow, hard fat, lanolin, beeswax, petroleum jelly, liquid paraffin, squalane, squalene, myristic acid, stearic acid, palmitic acid, cetanol, stearyl alcohol, 2-octyldodecanol, isopropyl myristate and octyldodecyl myristate, which can be used individually or in combinations of 2 or more.

[0013]

Examples of solvents for the local basic anesthetic hydrochloride used in the present invention, other than water, include solvents that have hydrophobic groups such as linear or cyclic hydrocarbons and hydrophilic groups such as hydroxyl groups, carboxyl groups, amino groups and polyoxyethylene groups. An example is crotamiton.

[0014]

Examples include propylene glycol, 1,3-butylene glycol, 3-methyl-1,3-butanediol, polyethylene glycol and other glycols, glycerin fatty acid ester, sorbitan fatty acid ester, polyoxyethylene hardened castor oil, polyoxyethylene glycol fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene alkyl ether and other surfactants.

[0015]

Examples of desirable solvents are clotramiton, and surfactants for oily ointments and suppositories, and 1,3-butylene glycol, purified water and polyethylene glycol for creams, aqueous gels and aqueous suppositories.

[0016]

Examples of desirable solvents will differ depending on the blend amount of local basic anesthetic hydrochloride, the type of solvent and the dosage form, but a range of 1-60 wt% with respect to the total amount of composition is generally preferred. It is desirable to prepare the composition by forming a liquid dispersion during formulation.

[0017]

Drugs other than local anesthetics can be blended in the composition of the present invention. There are no particular restrictions on these drugs, and examples include antiinflammatories such as prednisone acetate, prednisolone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone, dexamethasone, prednisolone valerate acetate and glycyrrhizic acid, vitamins such as tocopherol acetate, retinol acetate, retinol palmitate, ergocalciferol, pyridoxine hydrochloride, pyridoxamine hydrochloride, pyridoxamine phosphate, pyridoxal hydrochloride, pyridoxal phosphate, riboflavin, and riboflavin butyrate, antiphlogistic/pyrolytic analgesics such as aspirin, acetaminophenone [sic], phenacetin, diclofenac sodium, indometacin, mefenamic acid, aminopyrine and ibuprofen, anti-itch wound therapeutics such as lysozyme hydrochloride, allantoin and *arukurokisa* [Japanese composition containing aluminum chlorohydroxy allantoinate], sulfa drugs such as sulfadiazine, sulfisomizine, sulfisomizine sodium and formosulfamine, antibiotics or antifungal agents such as erythromycin, tetracycline, tetracycline hydrochloride, oxyetetracycline hydrochloride, streptomycin sulfate, gentamycin sulfate, fradiomycin sulfate, kanamycin sulfate, clotrimazole, miconazole and

miconazole nitrate, and bactericidal agents such as acrinol, alkylpolyaminoethyl glycine, isopropyl methyl phenol, cetylpyridinium chloride, dequalinium chloride, berberine chloride, benzalkonium chloride, cetrimide, chlorhexidine hydrochloride, chlorhexidine gluconate liquid, phenol and resorcin.

[0018]

With the composition of the present invention, the local basic anesthetic is dissolved in oil or fat, or lipophilic base that is miscible therewith, and the local basic anesthetic hydrochloride is separately dissolved or dispersed in solvent. The former solution and the latter solution or dispersion are then mixed, thus preparing a composition that contains the two substances stably and uniformly. If the oil or fat, or lipophilic base that is miscible therewith, is mixed beforehand with solvent, and local basic anesthetic and hydrochloride thereof are then added, the solubility with respect to the hydrochloride is dramatically reduced, which is undesirable in terms of obtaining a stable and uniform composition.

[0019]

When the uniform composition obtained in the manner described above is used locally, the local basic anesthetic and hydrochloride thereof are brought into uniform contact with the surface of the skin or membrane at the local site. Consequently, the rate of absorption or manifestation of action, as well as the persistence, can be easily controlled by selecting the type of agent or adjusting the concentration. This is extremely advantageous for achieving the objective of the present invention, which is to provide rapid and persistent manifestation of local anesthetic action.

[0020]

In addition, a stable local basic anesthetic composition having even better persistence and fast-acting effects is obtained by adjusting the blending ratio of local basic anesthetic and hydrochloride thereof in the aforementioned range.

[0021]

Working Examples

The present invention is described below by providing working examples and experimental examples.

[0022]

Working Example 1

Lidocaine	2.0 g
Dibucaine hydrochloride	0.16 g
Clotramiton	5 g
Miglyol 812	15 g
(product name; medium chain fatty acid triglycerides)	
Glycerin monostearate	2.5 g
White petroleum jelly	appropriate amount
total	100 g

The white petroleum jelly, glycerin monostearate, and Miglyol 812 were heated and dissolved, and lidocaine was added and dissolved. Separately, dibucaine hydrochloride was dissolved in heated clotramiton, and the solution was added to the former oil phase and mixed until uniform.

[0023]

Working Example 2

Lidocaine	1.5 g
Dibucaine hydrochloride	0.25 g
Clotramiton	5 g
Miglyol 812	15 g
(product name; medium chain fatty acid triglycerides)	
Glycerin monostearate	2.5 g
White petroleum jelly	appropriate amount

	total	100 g

The white petroleum jelly, glycerin monostearate and Miglyol 812 were heated and dissolved, and lidocaine was added and dissolved. Dibucaine hydrochloride was then dissolved in heated clotramiton, and this solution was added to the former oil phase and mixed until uniform.

[0024]

Working Example 3

Lidocaine	1.5 g
Dibucaine hydrochloride	0.25 g
Prednisolone hydrochloride	0.05 g
Tocopherol acetate	3 g
Allantoin	1 g
Clotramiton	5 g
Miglyol 812	
(product name; medium-chain fatty acid triglycerides)	10 g
Glycerin monostearate	5 g
White petroleum jelly	appropriate amount
total	100 g

The white petroleum jelly and glycerin monostearate were heated and dissolved, and the lidocane and tocopherol acetate were added and dissolved in heated Miglyol 812, and this solution was added and compounded in the former oil phase. Allantoin was then dispersed in Miglyol 812 and added. Separately, dibucaine hydrochloride and

prednisolone acetate were dissolved in heated clotramiton, and the solution was added and mixed uniformly in the former oil phase.

[0025]

Comparative Example 1

Lidocaine		3 g
Miglyol 812		
(product name; medium-chain fatty acid triglycerides)		15 g
Glycerin monostearate		2.5 g
White petroleum jelly		appropriate amount
	total	100 g

The white petroleum jelly, glycerin monostearate and Miglyol 812 were heated and dissolved, and lidocaine was then added and dissolved.

[0026]

Comparative Example 2

Dibucaine hydrochloride		0.5 g
Miglyol 812		15 g
(product name; medium-chain fatty acid triglycerides)		
Glycerin monostearate		2.5 g
White petroleum jelly		appropriate amount
	total	100 g

The white petroleum jelly, glycerin monostearate and Miglyol 812 were heated and dissolved. Separately, the dibucaine hydrochloride was dispersed using the Miglyol 812, and was added and mixed until uniform.

[0027]

Comparative Example 3

Lidocaine		3 g
Clotramiton		5 g
Miglyol 812		15 g
(product name; medium-chain fatty acid triglycerides)		
Glycerin monostearate		2.5 g
White petroleum jelly		appropriate amount
	total	100 g

White petroleum jelly, clotramiton, glycerin monostearate and Miglyol 812 were heated and dissolved, and lidocaine was then added and dissolved. The coefficients determined by dividing the amounts of local basic anesthetic (lidocaine) and local basic anesthetic hydrochloride (dibucaine hydrochloride) used in each of the examples above by the maximum allowed amounts (certified standards for topical hemorrhoid drugs), as well as the blending ratios and sum of the coefficients are shown in Table 2.

[0028]

Table 2

	Blend amount/maximum blend amount = coefficient		Blend ratio	Sum of the coefficients
	Lidocaine	Dibucaine hydrochloride		
Application Example 1	2.0/3 = 0.67	0.16/0.5 = 0.32	6.3:3	0.99
Application Example 2	1.5/3 = 0.5	0.25/0.5 = 0.5	3:3	1
Application Example 3	1.5/3 = 0.5	0.25/0.5 = 0.5	3:3	1
Comparative Example 1	3/3 = 1	--	3:0	1
Comparative Example 2	--	0.5/0.5 = 1	0:3	1
Comparative	3/3 = 1	--	3:0	1

Example 3				

*The blending ratios denote ratios found taking the hydrochloride as 3.

[0029]

Experimental Example 1

Corneas of male guinea pigs (body weight 180-300 g) were used, and surface analgesic action testing was carried out on the compositions of Application Examples 1 and 2 and Comparative Examples 1, 2 and 3. 20 mg of sample was applied to the cornea, and after a determinate period of time, the cornea was lightly stimulated 5 times with a mandolin wire, and the jerk reflex repetitions were measured. This measurement was performed twice, giving 10 as the stimulus number at each time point for a single sample. The onset time, used as an index of the rate of effect, was taken as the time of perfect jerk reaction results when no cornea jerk reactions occurred in any of the 10 trials. In addition, an anesthetic state was assumed in cases in which no cornea jerk reflex was seen in just one of the 10 trials, and the analgesic persistence time, used as an index of effect duration, was measured as the persistence time (duration). The results are shown in Table 3 and Figure 1.

[0030]

Table 3

Surface analgesic action experimental results

(n=10 average ± standard deviation) (units: min)

Sample name	Onset time	Duration
Application Example 1	0.50 ± 0.00	157.50 ± 4.73
Application Example 2	0.50 ± 0.00	185.50 ± 9.05
Comparative Example 1	0.50 ± 0.00	100.50 ± 4.97
Comparative Example 2	3.30 ± 0.21	89.00 ± 6.36
Comparative Example 3	0.50 ± 0.00	114.00 ± 7.85

[0031]

As is clear from Table 3 and Figure 1, the products of Working Examples 1 and 2 were equivalent to the products of Comparative Examples 1 and 3 and better than the

product of Comparative Example 2 in regard to the rate of the membrane surface analgesic action, and were superior to those of Comparative Examples 1-3 in regard to persistence.

[0032]

Effect of the invention

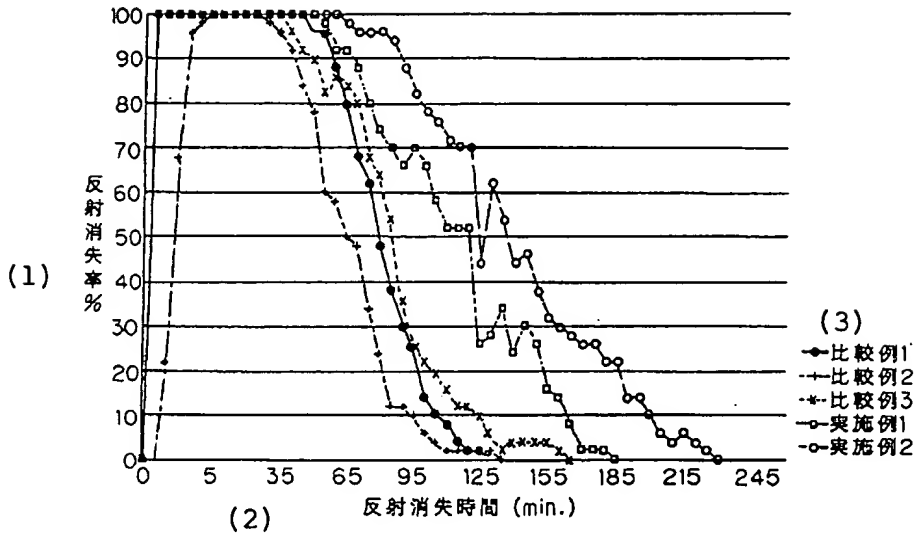
By means of the present invention, stable local anesthetic compositions are offered that are fast-acting and have good persistence. These compositions can be used, for example, as topical agents for locally reducing pain and itching at the surfaces of skin injuries, such as cuts, scrapes, scratches, acne, impetigo and facial carbuncles, at skin and connective tissue sites such as hemorrhoids, heat rash, sores, rashes, hives, insect bites, athletes foot and ringworm, and at sites of tooth pain.

[Brief description of the figures]

[Figure 1] Graph

Graph showing the results of comparative testing in Working Example 1.

Figure 1



Key:

1 Jerk reflex loss %

2 Jerk reflex extinction time (min)

3 Comparative Example 1

Comparative Example 2

Comparative Example 3

Working Example 1

Working Example 2

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A 61 K 31/165			A 61 K 31/165
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